Proceedings – 23rd Annual Conference – IEEE/EMBS Oct.25-28, 2001, Istanbul, TURKEY

NON-LINEAR COUPLING AMONG CARDIOVASCULAR VARIABILITY SIGNALS IN NEUROMEDIATE SYNCOPE

F. Censi[1], G. Calcagnini[1], S.Strano[2], P. Bartolini[1], V. Barbaro[1]
[1]Biomedical Engineering Laboratory, Istituto Superiore di Sanita', Roma, Italy
[2]Clinical Pathophysiology, La Sapienza University of Rome, Italy

Abstract- **Aim of this study is to evaluate the degree of coupling among the cardiovascular variability series and the respiration in subjects susceptible to neurally mediated syncope, in comparison to normal subjects. 21 patients susceptible to syncope and 10 sex and age matched control subjects have been enrolled in the study. ECG, respiration activity, and arterial blood pressure were simultaneously recorded at rest (controlled and free breathing) and during 70° head-up TILT test (free breathing). The degree of non-linear coupling among heart rate variability (HRV), blood pressure variability (BPV) and respiration has been quantified by means of a multivariate embedding-based approach. 11 patients developed syncope during the TILT test. The non-linear coupling among the cardiovascular variables and respiration turned out to be stronger during controlled breathing than during free breathing, both for TILT-positive and TILT-negative group. During late TILT phase, in the TILT-positive group, the non-linear coupling showed a significant increase. If the proposed non-linear coupling indexes can be considered expression of the coupling mechanisms involved in the vagal regulation of the cardiovascular system, an increase of the vagal tone accompanied by a decrease of the sympathetic activity seem to occur before a vasovagal event.**

Keywords **- Non-linear coupling, heart rate variability, cardiorespiratory coordination, neurally mediated syncope**

I. INTRODUCTION

Cardiovascular variables are characterized by pseudoperiodic oscillations reflecting the complex control mechanisms mediated by the autonomic nervous system. Over the last 20 years a great deal of research regarding short-term heart rate and blood pressure variability has been carried out in frequency domain [1][2][3]. This approach significantly helped to better understand the physiological meaning of the two main rhythms observed in heart rate and blood pressure fluctuations: a low frequency component (LF, 0.04-0.15 Hz) which is believed to be an expression of the baroreflex control, mediated by both sympathetic and parasympathetic branches, and a high frequency component (HF, 0.15-0.4 Hz) synchronous with respiration, generally considered a marker of the parasympathetic activity [4].

In parallel with the above linear approaches, the investigation of non-linear dynamics in heart rate variability have improved our understandings regarding the physiological and pathologically disturbed behaviors of the autonomic nervous system [5][6].

It should be kept in mind, however, that other physiological variables as well as external stimuli are involved in the autonomic nervous system-mediated regulation. The analysis of the interaction among these variables has indeed improved the knowledge about the autonomic functioning, even if applications of such analyses to investigate autonomic nervous system-linked pathologies are scarce. In addition, given the complexity of the mechanisms involved in the autonomic regulation, the analysis should take into account the non-linear features of the coupling between the involved variables.

Aim of this study is to evaluate the degree of coupling among the cardiovascular variability series and the respiration in subjects susceptible to neurally mediated syncope, in comparison to normal subjects. The degree of non-linear coupling has been quantified by means of a multivariate embedding-based approach, recently proposed by Hoyer et al. [7]. Particularly, we used two non-linear coupling indexes called independence of complexity (IC) and independence of predictability (IP).

II. METHODOLOGY

A. Experimental protocol and study population

ECG, respiration activity (RA), and arterial blood pressure (ABP) were simultaneously recorded at rest and during 70° head-up tilt test (figure 1). Surface ECG (II lead) was recorded by an analog electrocardiograph (MCR I, Esaote, Italy). APB was continuously and non-invasively recorded by photopletismographic technique (Finapres, Omheda, USA), and RA was monitored using a pletismographic thoracic belt. The signals were sampled in real-time (sampling frequency: 500 Hz, resolution: 12 bit, DT2801A, Data Translation, USA) and stored in a magneto-optical disk for further analysis. Data were collected in the Clinical Pathophysiology Unit of the University of Rome, 'La Sapienza'. All experiment were done in a light attenuated room starting from 2 PM.

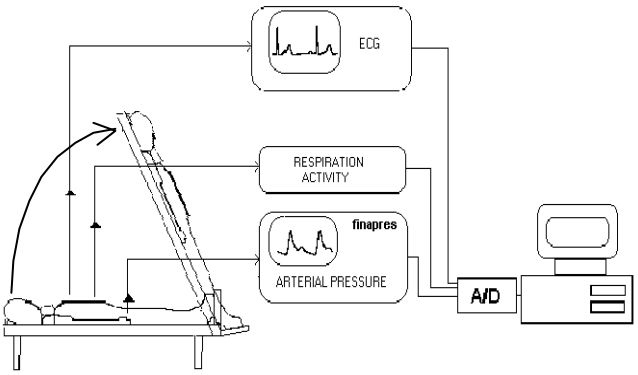

Fig. 1. Experimental setup.

In supine position, two 5-minute stages of controlled respiration have been performed (8 and 12 breaths/minute, 0.13 Hz and 0.20 Hz respectively), followed by a 5-minute

0-7803-7211-5/01$10.00©2001 IEEE

Report Documentation Page

Report Date	Report Type	Dates Covered (from... to)
25OCT2001	N/A	-

Title and Subtitle Non-Linear Coupling Among Cardiovascular Variability Signals in Neuromediate Syncope	**Contract Number**
	Grant Number
	Program Element Number
Author(s)	**Project Number**
	Task Number
	Work Unit Number
Performing Organization Name(s) and Address(es) Biomedical Engineering Laboratory, Istituto Superiore di Sanita, Roma, Italy	**Performing Organization Report Number**
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research, Development & Standardization Group (UK) PSC 802 Box 15 FPO AE 0949-1500	**Sponsor/Monitor's Acronym(s)**
	Sponsor/Monitor's Report Number(s)

Distribution/Availability Statement
Approved for public release, distribution unlimited

Supplementary Notes
Papers from the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, October 25-28, 2001, Istanbul, Turkey. See also ADM001351 for entire conference on cd-rom.

Abstract

Subject Terms

Report Classification unclassified	**Classification of this page** unclassified
Classification of Abstract unclassified	**Limitation of Abstract** UU

Number of Pages
4

stage of spontaneous respiration (REST, table I). Upright posture was maintained until the development of syncope or for a maximum duration of 40 minutes. Head-up tilt was defined positive if hypotension (systolic blood pressure lower than 80 mmHg), accompanied by slowing of the heart rate (lower than 40 bpm) developed. Subjects with syncope were quickly returned to the horizontal position. After return of patients to supine posture, a 5-minute recovery stage has been considered.

TABLE I
STAGES OF THE EXPERIMENTAL PROTOCOL

Stage	breaths/minute	Duration (minutes)
REST – supine position		
1	12	5
Instrumentation calibration	free	3
2	8	5
Instrumentation calibration	free	3
3	free	5
TILT – 70° head up tilt test		
4	free	≤ 40
RECOVERY – supine position		
5	free	5

The study population consisted of 21 patients (10 women) with two or more episodes of unexplained syncope during the preceding 6 months, and of 10 sex and age matched control subjects. No patients had evidence of structural heart disease or diabetes. Patients' average age was 24±7 years (range: 14÷44).

B. Data pre-processing

The low-pass filtered event series (ES) was used to extract the heart rate variability (HRV) signal since it is a reliable time domain representation with high temporal resolution. In ES each beat is replaced by a δ function; the signal can be described as:

$$x(t) = \sum_{k=0}^{N-1} \delta(t - t_k)$$

where δ is the Dirac delta function, t_k is the occurrence time of the k^{th} beat and N is the total number of beats. To obtain the heart rate variability series, the ES was low-pass filtered at 0.5 Hz and re-sampled at 2 Hz [8]. Correspondingly, blood pressure variability (BPV) and RA series were obtained by a similar low-pass filtering procedure (FIR, 10 order, cut-off frequency 0.5 Hz) and a re-sampling at 2 Hz of the ABP and RA, respectively. According to this procedure, HRV and RA series were expressed in arbitrary units (a.u.), and BPV in mmHg. This approach particularly guarantees the time synchronization between HRV, BPV and RA.

C. *Non-linear coupling quantification*

The non-linear coupling quantification is based on a multivariate embedding approach. The multivariate embedding procedure allows for the reconstruction of the joint behaviour of multiple systems which are more or less dependent [5][9]. According to the Takens' reconstruction theorem [10], the dynamics of a system can be reconstructed by taking the time-delayed values of one single observed time series. The joint system dynamics of two coupled subsystems (x(t) and y(t)) can be reconstructed by an analogous delay vector - q(t) - using values of the two contributing subsystems, as follows:

q(t) = [x(t), x(t-τ), x(t-2τ), … , x(t-mτ), y(t), y(t-τ), y(t-2τ), …, y(t-nτ)]

where x(t) and y(t) have embedding dimension *m* and *n* respectively, and the joint embedded system has dimension *m+n*.

The method consist on the computation of the correlation dimension (CD) and of the correlation entropy (CE) for the individually embedded series (x(t) and y(t)) as well as for the jointly embedded series (q(t)), and on the comparison of the obtained values. CD and CE have been estimated according to the Grassberger-Procaccia method for the estimation of the correlation integral [11]. The correlation integral counts for the number of pairs of points $x(t_i)$,$x(t_j)$ which are separated by a distance less than ε in a phase-space of embedding dimension *m*, according to the following formula:

$$C(\varepsilon, m) = \frac{1}{N'^2} \sum_{i=1}^{N'} \sum_{j=i+1}^{N'} H(\varepsilon - |x(t_i) - x(t_j)|)$$

where N'=N-m+1, N is the number of points of the time series, and H is the Heaviside step function (H(y)=0 for y≤0, and H(y)=1 for y>0).

We estimated CD as the slope of the log-log plot of C(ε,m) vs. ε in the scaling region, as follows [9]:

$$CD_m(\varepsilon) = \frac{d \log C(\varepsilon, m)}{d \log \varepsilon}$$

In the scaling region CD is independent of ε and *m*. Since in physiological data sets no convincing scaling region exists, we performed the comparison of different time series by using appropriate standard values of ε and *m* [5]. CE was estimated as:

$$CE_m(\varepsilon) = \frac{1}{t} \ln \frac{C(\varepsilon, m)}{C(\varepsilon, m+1)}$$

where ε and *m* were chosen according to the CD estimation.

IC has been extracted by combining the CDs of each individually embedded series (CD_x and CD_y) with that of the jointly embedded signal (CD_q), as follows [7]:

$$IC = \frac{|CD_q - CD_x| + |CD_q - CD_y|}{CD_x + CD_y}$$

Similarly, IP has been extracted by combining the CE values as follows [7]:

$$IP = \frac{|CE_q - CE_x| + |CE_q - CE_y|}{CE_x + CE_y}$$

Both indexes vary between 0 and 1. 0 indicates fully coupled quantities and 1 stands for completely independent variables. By means of these indexes, we estimated the non-linear coupling between HRV and respiration, BPV and respiration, and HRV and BPV.

In this work, approximate (coarse-grain) correlation dimension and correlation entropy have been calculated for an embedding dimension *m*=10 (*m*=20 for the joint embedded vector) and a distance *r* equal to 10% the maximum distance

of points in the phase space. The time delay τ has been chosen according to the first zero of the auto-correlation function of each series, which for the analyzed series corresponds to about one quarter of the characteristic period (τ=10).

III. RESULTS

11 out of 21 subjects developed syncope during head-up TILT test. The TILT-positive subjects developed pallor, diaphoresis, dizziness and/or transient loss of consciousness within 5 to 15 minutes of head-up TILT. The TILT was terminated when systolic blood pressure fell below 80 mmHg or when HR fell below 40 bpm. All subjects recovered spontaneously on return to the supine position.

The coupling between respiration, HRV and BPV has been analyzed during the two controlled breathing stages (5 minutes each), during REST (5 minutes), TILT, and the recovery phase. Because the period of upright TILT varied in duration among patients with syncope depending on whether symptoms developed and the time that syncope occurred, total duration of upright posture in each patient or subject was divided into 3 intervals indicated as: early TILT, middle TILT and late TILT (which corresponds to pre-syncope in TILT positive group). The recovery phase started after return of the patient to supine posture and lasted 5 minutes (figure 2). Linear coupling has been quantified as the maximum of the cross-correlation function.

Figure 3 shows the values of the coupling indexes (IC, IP and cross-correlation) between HRV and respiration (HRV/respiration) in the 7 phases of the protocol, for the

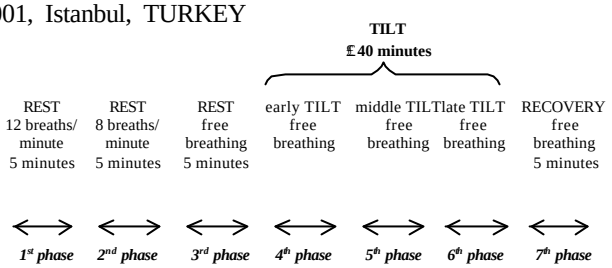

Fig. 2. Phases of the experimental protocol.

TILT-positive subjects (left panel) and for the TILT-negative group (right panel) expressed as mean ± standard deviation. The results obtained for the TILT-negative group are not significantly different from those obtained for the control group.

The non-linear coupling indexes show that the coupling is significantly stronger during the 8 breaths/minute stage than during 12 breaths/minute stage for both TILT-positive and TILT-negative group ($p<0.01$). In addition, during controlled respiration, the coupling is significantly higher than during free breathing at REST for both groups ($p<0.01$). From REST condition to early and middle TILT, the coupling does exhibit a significant decrease for both groups for HRV/respiration, BPV/respiration ($p<0.01$). During late TILT phase, in the TILT-positive group the non-linear coupling has a significant increase ($p<0.01$) and during the recovery phase it returns to values similar to that observed during the REST phase. Linear coupling does not significantly vary in the TILT phases.

Similar results have been obtained for the coupling

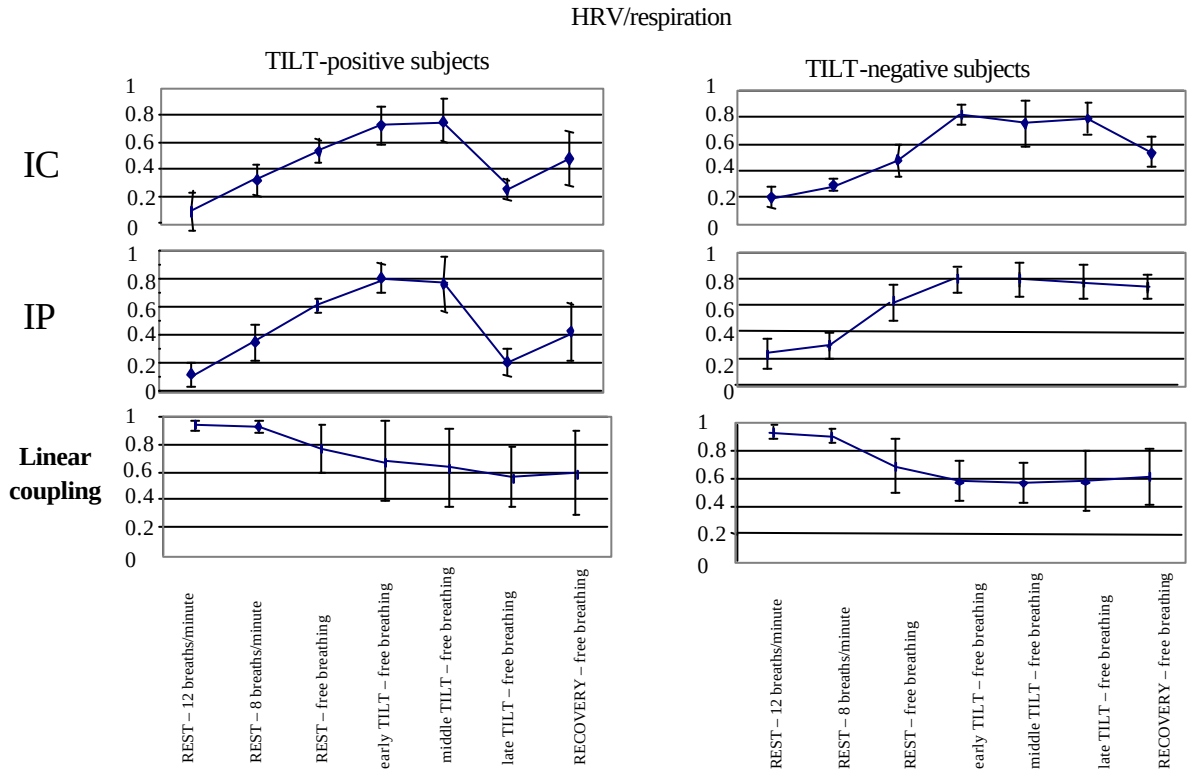

Fig. 3. Coupling between HRV and respiration: non-linear indexes values during the phases of the controlled breathing and TILT-test protocol, for the TILT-positive subjects (left panel) and the TILT-negative group (right panel). Dashed line denotes the increase of the coupling strenght during the late TILT phase (or pre-syncope) for the TILT-positive subjects.

BPV/respiration and HRV/BPV (not shown).

No significant difference has been observed between TILT-positive and TILT-negative group during controlled breathing, and free breathing at REST and during early and middle TILT. Of course the difference does reach a statistical significance during late TILT ($p<0.01$).

The LF/HF ratio, computed during the free breathing REST phase and during the 3 TILT phases, was not different between the 2 groups in all phases. During REST its value is significantly different from that obtained in the early TILT, for both groups ($p<0.01$). However, during early TILT phase the values obtained for LF/HF ratio widely vary among patients. During late TILT, the LF/HF ratio is not different from the preceding TILT phases.

IV. DISCUSSION

The results obtained from this investigation show an increase of the non-linear coupling between cardiovascular variability signal and respiration in concomitance with a syncope event, which cannot be detected by traditional linear methods. Since the autonomic nervous system, governing the links between heart rate, blood pressure and respiration, is a complex system, it is not surprising that a deeper non-linear analysis of the coupling among the contributing subsystems provides significant results.

Since respiration is usually closely coupled to heart rate, the cardiorespiratory coupling could be of paramount importance for the understanding of the underlying pathogenic mechanisms, as well as for the choice of the proper therapeutic approach. During controlled and free breathing at REST, the cardiorespiratory coupling (HRV/respiration and BPV/respiration) did not differ between TILT-positive and TILT-negative subjects. This finding is consistent with the previous results obtained by Lipsitz *et al.* [12], and indicates that the baseline cardiorespiratory coordination is not altered in subjects susceptible to syncope. Similar results have been found during early and middle TILT, suggesting an adaptation of the cardiorespiratory dynamics at the beginning of the head-up TILT test. In addition, during the first 2 TILT phases, the non-linear coupling between both HRV and respiration and BPV and respiration resulted to be significantly lower than that observed during REST. This finding is somehow consistent with the de-coupling found by Lipsitz *et al.* 3 minutes before syncope, and suggests a dissociation between respiration and cardiovagal activity during the first 2 TILT phases probably associated with the increase of the sympathetic tone [2].

One possible explanation for the dissociation between respiration and heart rate variability could be the high sympathetic tone during tilt that suppresses the respiratory sinus arrhythmia until sympathetic withdrawal before syncope allows respiratory sinus arrhythmia to increase. Since the non-linear coupling between HRV and respiration is likely considered the expression of the parasympathetic outflow to the heart, the progressive decrease of the non-linear coupling from REST to TILT could be the expression of the shift in the balance between sympathetic and parasympathetic activity. Particularly, if the proposed non-linear coupling indexes can be considered expression of the coupling mechanisms involved in the vagal regulation of the cardiovascular system, an increase of the vagal tone accompanied by a decrease of the sympathetic activity seem to occur before a vasovagal event.

REFERENCES

[1] A. Malliani, M. Pagani, F. Lombardi, S. Cerutti, "Cardiovascular neural regulation explored in the frequency *Circulation*, vol. 84, pp. 482-492, 1991.

[2] S. Akselrod, D. Gordon, F.A. Ubel, D.C. Shannon, A.C. Berger, R.J. Cohen, "Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control," *Science* vol. 10;213(4504), pp.220-222, 1981.

[3] M. Pagani, F. Lombardi, S. Guzetti, O. Rimidli, R. Furlan, P. Pizzinelli, G. Sandrone, G. Malfatto, S. Dell'Orto, E. Piccaluga, M. Turiel, G. Baselli, S. Cerutti, A. Malliani, "Power spectral analysis of a beat-to-beat heart rate and blood pressure variability as a possible marker of symphato-vagal interaction in man and conscious dog," *Circ.Res*. vol. 59, pp. 178-193, 1986.

[4] Task Force, Heart Rate Variability, "Standard of measurement, physiological interpretation and clinical use," *Circulation*, vol 93, pp. 1043-1065, 1996.

[5] D. Hoyer, K. Schmidt, U. Zwiener, R. Bauer, "Characterization of complex heart rate dynamics and their pharmacological disorders by non-linear prediction and special data transformation," *Cardiovascular Research*, vol. 31, pp. 434-440, 1996.

[6] U. Zwiener, D. Hoyer, R. Bauer, B. Luethke, B. Walter, *et al.,"*Deterministic-chaotic and periodic properties of heart rate and arterial blood pressure fluctuations and their mediations in piglets," *Cardiovascular research*, vol. 31, pp. 455-456, 1996.

[7] D. Hoyer, R. Bauer, B. Walter, U. Zwiener, "Estimation of non-linear couplings on the basis of complexity and predictability - a new method applied to cardiorespiratory coordination," *IEEE Trans. BME*, vol. 45, pp. 1-8, 1998.

[8] R.W. De Boer, J.M. Karemaker, J. Strackee, "Comparing spectra of a series of point events particularly for heart rate variability data", *IEEE Trans. BME* vol. 31, pp. 384-387, 1984.

[9] D. Hoyer, D. Kaplan, F. Schaaff, M. Eiselt, "Determinism in bivariate cardiorespiratory phase-space sets," *IEEE Eng. Med. Biol.*, vol 17(6), pp. 26-31, 1998.

[10] F. Takens, "Detecting strange attractor in turbolence," in *Dynamical systems in turbolence*, D. Rand and S. Young, Eds. New York: Springer-Verlag, 1980, pp. 366-381.

[11] P. Grassberger, P. Procaccia, "Measuring the strangeness of strange attractor," *Physica D*, vol. 9, pp. 189-207, 1983.

[12] L.A. Lipsitz, J. Hayano, S. Sakata, A. Okada, R.J. Morin, "Complex demodulation of cardiorespiratory dynamics preceding vasovagal syncope," *Circulation*, vol. 8;98(10), pp. :977-983, 1998.